REMARKS

Reconsideration and withdrawal of the rejections of this application and consideration and entry of this paper are respectfully requested in view of the herein amendment and remarks, which place the application in condition for allowance.

I. STATUS OF CLAIMS AND FORMAL MATTERS

Claims 1, 2, 18, and 29-33 are pending in this application. Claim 1 is amended and claims 8, 35, and 36 are newly cancelled without prejudice, without admission, without surrender of subject matter and without intention of creating any estoppel as to equivalents.

Support for the amendments of claim 1 can be found throughout the specification as originally filed and amended, and in the previously pending claims. For instance, the amendment to recite APC surface molecules and Notch ligands can be found, as an example, on page 13, lines 5-10, and on page 48, line 26 – page 50, line 49 in the specification as originally filed; on page 38, lines 25-30 in the specification as amended on June 28, 2004; and in claims 35 and 36 as previously pending. The amendment to recite "comprising a variable region" can be found, for instance, on page 6, lines 23-24, of the specification as originally filed. No new matter is added.

It is respectfully submitted that the claims, herewith and as originally presented, are patentably distinct over the prior art cited by the Examiner, and that these claims are and were in full compliance with the requirements of 35 U.S.C. §112. The amendments to the claims, as presented herein, are not made for purposes of patentability within the meaning of 35 U.S.C. §§§§ 101, 102, 103 or 112. Rather, these amendments and additions are made simply for clarification and to round out the scope of protection to which Applicants are entitled.

II. THE REJECTIONS UNDER 35 U.S.C. 112 ARE OVERCOME

Initially, Applicants note that claim 8 is cancelled, thereby rendering all rejections against claim 8 moot.

Enablement

Claims 1, 2, 8, 29, and 31 were rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the enablement requirement. This rejection is traversed.

Initially, Applicants draw attention to the instant claims, wherein claim 1, from which the other claims depend, recites "[a] conjugate comprising a first sequence and a second sequence, wherein: the first sequence comprises an antibody or antibody fragment comprising a variable region and which binds to an antigen presenting cell (APC) surface molecule, wherein the APC surface molecule is selected from the group consisting of an MHC class II molecule, CD205 (DEC205), CD204, CD14, CD206, TLRs, Langerin (CD207), DC-SIGN (CD209), CD68, CD83, CD33, CD54 and BDCA-2,3,4; and the second sequence comprises a Notch ligand or a fragment thereof, wherein the second sequence comprises a Notch ligand DSL domain and at least one EGF-like repeat, wherein the Notch ligand is selected from the group consisting of human Delta 1 comprising the amino acid sequence of SEQ ID NO: 40, human Delta 3 comprising the amino acid sequence of SEQ ID NO: 41, human Delta 4 comprising the amino acid sequence of SEQ ID NO: 42, human Jagged 1 comprising the amino acid sequence of SEQ ID NO: 43, and Jagged 2 comprising the amino acid sequence of SEQ ID NO: 44, and wherein the second sequence retains Notch signalling activity." With this in consideration, Applicants assert that the instant claims are enabled by the specification.

Firstly, Applicants submit that the specification provides substantial guidance for the instant claims. For instance, the components of the claimed conjugate of claim 1 are described on page 3, lines 3-8, while the APC surface molecules recited in claim 1 are discussed on page 12, lines 17-19, and on page 13, lines 5-10. Notably, the specification describes polypeptides which can bind to MHC Class II molecules on page 39, line 18 – page 41, line 24. Further, the Notch ligand recited in claim 1 is disclosed on page 48, line 26 – page 50, line 49 of the specification as originally filed, and on page 38, lines 25-30 in the specification as amended on June 28, 2004. In addition, the working examples demonstrate how to prepare a conjugate comprising N-terminal 90 amino acids of TSST-1 and an N-terminal fragment of human Jagged1. Based on these teachings, one of ordinary skill in the art can prepare the scope of conjugates encompassed by the instant claims.

The Office Action recites that "until the surface molecule on APC has been identified, the antibody or binding fragment that binds to such surface molecule then can be made using such molecule as an antigen" (see Office Action, page 7). Applicants note that the instant claims indeed identify the APC surface molecule, and therefore the corresponding antibody or binding fragment can be made. Moreover, the Office Action recites that "the specification does not teach

which 'fragment of which Notch Ligand' retains Notch signaling activity other than the specific fragment recited in claim 36" (see Office Action, page 6). Applicants point out that the instant claims indeed recite the Notch ligands formerly presented in claim 36. Hence, the skilled artisan can arrive at the claimed conjugate.

Applicants additionally submit that the Office Action concedes that the specification is enabling for "(1) a conjugate comprising an antibody or antigen binding fragment thereof which binds to an APC surface molecule selected from the group consisting of CD205 (DEC205), CD204, CD 14, CD206, TLR, Langerin (CD207), DC-SIGN (CD209), CD68, CD83, CD33, CD54, BDCA-2, BDCA-3, BDCA-4 wherein the antibody or binding fragment thereof is conjugated to a human Notch ligand selected from the group consisting of human Delta1 comprising the amino acid sequence of SEQ ID NO: 40, human Delta 3 comprising the amino acid sequence of SEQ ID NO: 41, human Delta 4 comprising the amino acid sequence of SEQ ID NO: 42, human Jagged 1 comprising the amino acid sequence of SEQ ID NO: 43, Jagged 2 comprising the amino acid sequence of SEQ ID NO: 44, a human Notch ligand fragment selected from the group consisting of the amino acid sequence of SEQ ID NO: 25, SEQ ID NO: 29, SEQ ID NO: 32, SEQ ID NO: 36, SEQ ID NO: 38 and SEQ ID NO: 39 wherein the fragment retains Notch signaling activity" (see Office Action, paragraph bridging pages 3 and 4). Applicants point out that instant claim 1 recites antibody and antibody fragments and Notch ligands that the Office Action has deemed enabled.

With this consideration, Applicants assert that instant claim 1, as well as claims 2, 29, and 31 which depend therefrom, are enabled by the specification. Accordingly, Applicants request reconsideration and withdrawal of the rejection under Section 112, first paragraph, pertaining to enablement.

Written Description

Claims 1, 2, 8, 29, and 31 were rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the written requirement. This rejection is traversed.

As discussed above, instant claim 1, from which claims 2, 29, and 31 depend, recites APC surface molecules to which antibody or antibody fragment binds, and recites Notch ligands Therefore, the instant claims do **not** encompass "any 'first sequence comprising any antibody or any antibody fragment that binds to any APC' and second sequence such as any Notch ligand fragment comprises a DSL domain and one or more EGF-like repeat wherein the second

sequence retains Notch signaling activity without the amino acid sequence" (see Office Action, page 10); rather, the instant claims provide a structure of the claimed conjugate.

Claim 35 is rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement, because the Office Action contended that the specification discloses only superantigen, and not antibody or antibody fragment, as being capable of binding to MHC class II molecule on APC. Applicants note that claim 35 is cancelled, thereby rendering its rejection moot.

However, Applicants note that the specification indicates that proteins that bind to MHC class II molecules, other than superantigens, may be developed or discovered. For example, the specification recites "[i]t will be appreciated that one can apply conventional protein binding assays to identify molecules which bind to APC surface molecules. It will also be appreciated that one can apply structural-based drug design to develop sequences which bind to APC surface molecules" (specification, page 13, lines 18-21). Thus, the specification teaches that proteins that may bind to APC surface molecules such as MHC class II molecules are not restricted to superantigens. Consequently, claim 35 is supported in the specification.

Accordingly, Applicants request reconsideration and withdrawal of the rejection under Section 112, first paragraph, pertaining to written description.

Indefiniteness

Claims 2 and 29 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. The Office Action contended that a conjugate involves chemical coupling of two proteins, and therefore any reference of the term "conjugate" as a product of transformation of a host cell is improper.

In response, Applicants respectfully disagree. Applicants remind that, according to MPEP § 2111.01(IV), "applicant is entitled to be his or her own lexicographer." With this in mind, Applicants draw attention to specification as originally filed, page 26, lines 3-10, which recites that "[c]onjugates of the invention can be recovered and purified from recombinant cell cultures by well-known methods. . . " Hence, the term "conjugate" as used in the specification and the claims encompasses a product of chemical coupling as well as a product of transformation of a host cell. Therefore, instant claims 2 and 29 are not indefinite.

Accordingly, Applicants request reconsideration and withdrawal of the rejection under Section 112, second paragraph.

III. THE REJECTIONS UNDER 35 U.S.C. 102 ARE OVERCOME

Initially, Applicants note that claims 8, 35, and 36 are cancelled, thereby rendering all rejections against claim 8 moot.

Applicants also respectfully point out that "[a] rejection for anticipation under section 102 requires that each and every limitation of the claimed invention be disclosed in a single prior art reference." *In re Buszard* 504 F.3d 1364, 1366 (Fed. Cir. 2007) (citing *In re Paulsen,* 30 F.3d 1475, 1478-79 (Fed. Cir. 1994); *Karsten Mfg. Corp. v. Cleveland Golf Co.,* 242 F.3d 1376, 1383 (Fed. Cir. 2001) ("Invalidity on the ground of 'anticipation' requires lack of novelty of the invention as claimed . . . that is, all of the elements and limitations of the claim must be shown in a single prior reference, arranged as in the claim.")).

WO 98/20142

Claims 1, 2, 8, 29, 31, and 35 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by WO 98/20142. This rejection is traversed.

As discussed above, instant claim 1 clarifies that the first sequence of the conjugate comprises "an antibody or antibody fragment comprising a variable region and which binds to an antigen presenting cell (APC) surface molecule, wherein the APC surface molecule is selected from the group consisting of an MHC class II molecule, CD205 (DEC205), CD204, CD14, CD206, TLRs, Langerin (CD207), DC-SIGN (CD209), CD68, CD83, CD33, CD54 and BDCA-2,3,4," and that the second sequence "comprises a Notch ligand DSL domain and at least one EGF-like repeat, wherein the Notch ligand is selected from the group consisting of human Delta 1 comprising the amino acid sequence of SEQ ID NO: 40, human Delta 3 comprising the amino acid sequence of SEQ ID NO: 41, human Delta 4 comprising the amino acid sequence of SEQ ID NO: 42, human Jagged 1 comprising the amino acid sequence of SEQ ID NO: 43, and Jagged 2 comprising the amino acid sequence of SEQ ID NO: 44." WO 98/20142 does not teach antibody or antibody fragments that comprise a variable region as recited in claim 1, as WO 98/20142 relates to fusion proteins having IgG F_c antibody fragments for binding to APC F_c receptors (*see* WO 98/20142, page 8, lines 9-11, and page 16, lines 3-7). In addition, WO 98/20142 does not teach APC surface molecules as recited in claim 1. Hence, WO 98/20142 does not teach each and every limitation of instant claim 1.

Notably, instant claim 1 incorporates, in part, Notch ligands recited in former claim 36. Claim 36 was not cited in the rejection as being anticipated by WO 98/20142.

Hence, Applicants assert that WO 98/20142 does not anticipate claim 1, or claims 2, 29, and 31, which depend therefrom.

EP 08618946

Claims 1, 2, 8, 29, 31, and 36 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by EP 0861894. This rejection is traversed.

Instant claim 1 clarifies that the first sequence of the conjugate comprises an antibody or antibody fragment which binds to an antigen presenting cell (APC) surface molecule, wherein the APC surface molecule is selected from the group consisting of an MHC class II molecule, CD205 (DEC205), CD204, CD14, CD206, TLRs, Langerin (CD207), DC-SIGN (CD209), CD68, CD83, CD33, CD54 and BDCA-2,3,4. In contrast, EP 0861894 relates to a chimeric fusion protein comprising an antibody fragment that binds to CD32 receptor, and a Notch ligand. EP 0861894 does not teach any of the APC surface molecules recited in instant claim 1. Further, the antibody fragment of EP 0861894 is an F_C domain rather than a variable region as recited in instant claim 1 (*see* EP 0861894, page 10, lines 4-8, page 16, lines 3-24).

Therefore, EP 0861894 fails to teach each and every element of the claimed invention, and thereby does not anticipate claim 1, or claims 2, 29, and 31 that depend therefrom.

U.S. Patent No. 6,664,098

Claims 1, 2, 8, 29, 31, and 36 were rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 6,664,098. This rejection is traversed.

As discussed above, instant claim 1 clarifies that the first sequence of the conjugate comprises an antibody or antibody fragment which binds to an antigen presenting cell (APC) surface molecule, wherein the APC surface molecule is selected from the group consisting of an MHC class II molecule, CD205 (DEC205), CD204, CD14, CD206, TLRs, Langerin (CD207), DC-SIGN (CD209), CD68, CD83, CD33, CD54 and BDCA-2,3,4. On the other hand, U.S. Patent No. 6,664,098 relates to a fusion protein comprising human IgG F_c that binds to CD32 receptor, and a Notch ligand (U.S. Patent No. 6,664,098, col. 11, lines 57-65, and col. 21, lines 30-53). U.S. Patent No. 6,664,098 does not teach antibody or antibody fragments that comprise a variable region or any of the APC surface molecules recited in instant claim 1.

Therefore, Applicants assert that U.S. Patent No. 6,664,098 fails to teach each and every element of the claimed invention and, thus, does not anticipate claim 1, or dependent claims 2, 29, and 31.

Accordingly, Applicants request reconsideration and withdrawal of the rejections under Section 102.

IV. THE REJECTIONS UNDER 35 U.S.C. 103 ARE OVERCOME

Claims 1 and 35 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over WO 98/20142 in view of Snider et al. (J Immunol 1987, 139: 1609-1616), U.S. Patent Publication No. 2003/0148316, Wollenberg et al. (J Invest Dermatol 2002, 118: 327-334), and/or Noorman et al. (J Leukocyte Biol 1997, 61: 63-72). Claims 1 and 36 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over WO 98/20142 in view of Snider et al., U.S. Patent Publication No. 2003/0148316, Wollenberg et al., Noorman et al., or U.S. Patent No. 6,664,098 or U.S. Patent No. 6,136,952. These rejections are traversed and will be addressed collectively.

Applicants note that claims 35 and 36 are cancelled, thereby rendering their rejection moot.

To reiterate, instant claim 1, from which the other claims depend, recites "[a] conjugate comprising a first sequence and a second sequence, wherein: the first sequence comprises an antibody or antibody fragment comprising a variable region and which binds to an antigen presenting cell (APC) surface molecule, wherein the APC surface molecule is selected from the group consisting of an MHC class II molecule, CD205 (DEC205), CD204, CD14, CD206, TLRs, Langerin (CD207), DC-SIGN (CD209), CD68, CD83, CD33, CD54 and BDCA-2,3,4; and the second sequence comprises a Notch ligand or a fragment thereof, wherein the second sequence comprises a Notch ligand DSL domain and at least one EGF-like repeat, wherein the Notch ligand is selected from the group consisting of human Delta 1 comprising the amino acid sequence of SEQ ID NO: 40, human Delta 3 comprising the amino acid sequence of SEQ ID NO: 41, human Delta 4 comprising the amino acid sequence of SEQ ID NO: 42, human Jagged 1 comprising the amino acid sequence of SEQ ID NO: 43, Jagged 2 comprising the amino acid sequence of SEQ ID NO: 44, and a human Notch ligand fragment comprising a DSL domain with an amino acid sequence selected from the group consisting of the amino acid sequences shown in Figure 9, and wherein the second sequence retains Notch signaling activity."

As described above, WO 98/20142 does not disclose the APC surface molecules recited in instant claim 1. The Office Action relies on Snider et al., U.S. Patent Publication No.

2003/0148316, Wollenberg et al., and/or Noorman et al. as allegedly relating to APC surface molecules, and U.S. Patent No. 6,664,098 or U.S. Patent No. 6,136,952 as allegedly relating to Notch ligands, in order to arrive at the claimed invention. However, none of these references remedy how WO 98/20142 teaches away from the claimed invention.

Applicants note that, for an invention to be obvious, a person of ordinary skill in the art would have had reason to attempt to make the composition or device, or carry out the claimed process, and would have had a reasonable expectation of success in doing so. *Pharmastem Therapeutics, Inc. v. Viacell, Inc.* 491 F.3d 1342, 1360 (2007) (quoting *KSR*, 127 S. Ct. 1727, 1740 (a combination of elements "must do more than yield a predictable result"; combining elements that work together "in an unexpected and fruitful manner" would not have been obvious)). With this in mind, Applicants assert that there would be no reason to make the claimed conjugate, as the skilled artisan would not be motivated to combine these cited references.

Applicants reiterate that the claimed invention relates to a conjugate comprising a first sequence that comprises an antibody or antibody comprising a variable region; the antibody or antibody fragment will thereby bind to the APC surface molecule via its variable domain. In contrast WO 98/20142 relates to fusion proteins which have IgG F_c antibody fragments for binding to APC F_c receptors. Hence, WO 98/20142 teaches away from the claimed invention and to conjugates that bind to APC due to the presence of an antibody variable domain. There would be no motivation to use WO 98/20142 or to combine WO 98/20142 with the other cited references to arrive at the claimed invention.

In addition, according to the Office Action, Snider et al. relates to a method of targeting antigen to APC using antigen conjugated antibody that binds to a protein antigen or cell marker such as MHC class II or F_c gamma receptor expressed on APC. However, Snider et al. requires the use of crosslinked antibodies, which is in contrast to WO 98/20142. Also, Snider et al. relates to the use of antibodies with antigens rather than antibodies with cell signaling molecules. Given these differences between WO 98/20142 and Snider et al., one of ordinary skill in the art would not be motivated to combine them.

Moreover, U.S. Patent Publication No. 2003-0148316 relates to methods and compositions regarding a dendritic cell expression database, and indicates that mannose receptor is expressed on APC. Wollenberg et al. relates to the use of anti-CD206 antibodies to investigate

None of these cited references relate to using the antibodies to generate a construct as disclosed in the claimed invention.

Applicants remind that "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR*, 127 S. Ct. 1727, 1741. Here, even if U.S. Patent Publication No. 2003-0148316, Wollenberg et al., and Noorman et al. relate to APC surface molecules, it does not render the claimed invention obvious. In the absence of impermissible hindsight, there would be no motivation to combine any of these references, which relate to a different use, with the product in WO 98/20142.

U.S. Patent No. 6,664,098 and U.S. Patent No. 6,136,952 relate to Notch ligand. There would be no motivation to combine these references with WO 98/20142. U.S. Patent No. 6,664,098 relates to fusion proteins having an F_C domain rather than a variable region as recited in instant claim 1, and thereby teaches away from the claimed invention. U.S. Patent No. 6,136,952 relates to cloning human Jagged and a method of diagnosing Alagille syndrome. There is no teaching or suggestion of using Jagged polypeptides to generate a construct as claimed.

Further, even if U.S. Patent No. 6,664,098 and U.S. Patent No. 6,136,952 were combined, they would still fail to teach or suggest any of the APC molecules of the claimed invention. As discussed above, there would be no motivation to combine any of Snider et al., U.S. Patent Publication No. 2003-0148316, Wollenberg et al., or Noorman et al. with WO 98/20142. Similarly, there would be no motivation to combine any of Snider et al., U.S. Patent Publication No. 2003-0148316, Wollenberg et al., or Noorman et al. with U.S. Patent No. 6,664,098 or U.S. Patent No. 6,136,952.

Hence, the combinations of cited references as discussed here fail to render claim 1 as obvious. Accordingly, Applicants request reconsideration and withdrawal of the rejections under Section 103.

REQUEST FOR INTERVIEW

If any issue remains as an impediment to allowance, an interview with the Examiner and her SPE are respectfully requested and the Examiner is additionally requested to contact the undersigned to arrange a mutually convenient time and manner for such an interview.

CONCLUSION

In view of the remarks and amendments herewith, the application is in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited. The undersigned looks forward to hearing favorably from the Examiner at an early date, and, the Examiner is invited to telephonically contact the undersigned to advance prosecution.

Respectfully submitted,

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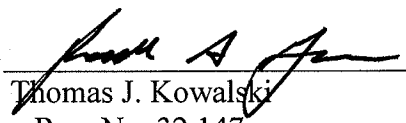
By: 

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